Comparing the performance of gene expression assays in breast cancer

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Comparing the performance of gene expression assays in breast cancer.

Response to Letter to the Editor

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Dear Editor:

We appreciate Dr. Suthers' comments on our recent paper regarding risk score classification and interpretation of multigene tests in early breast cancer (1).

We fully agree with Dr. Suthers' arguments that differential risk classification of multigene tests alone is not equal to differential power of the individual assays to predict chemotherapy response. Sufficiently powered prospective randomized clinical trials are the highest level of evidence to demonstrate a relationship between risk score classification and the predictive value of treatment benefit for multigene tests in early breast cancer. Among the five multigene tests addressed in our paper, only the 70-gene Mammaprint (MMP) and the 21-gene Recurrence Score (RS) assays have been validated in prospective randomized clinical trials (2,3). The TailorX clinical trial demonstrated the predictive power of RS for the lack of chemotherapy benefit in the low- and intermediate risk groups. The MINDACT trial demonstrated that high clinical risk/low genomic risk MMP patients had at least a 92% chance of being free of distant metastases at 5 years of follow-up without chemotherapy; it was not powered to determine chemotherapy benefit, and one cannot exclude such a benefit in these patients (3,6). Dr. Suthers correctly notes that TailorX included more patients from the clinically low risk than high risk category, and the biological link between response and parameters other than RS such as immunohistochemistry (IHC) and histological features has not been reported (2).

IHC for hormone receptors (ER, PR), HER2 and Ki67 as well as histological features as tumor grade, size and nodal status provide prognostic information in all breast cancer patients and predictive power to determine adjuvant therapy options (e.g. endocrine and HER2-targeted therapies) in most but not all patients. The TailorX study set out to address a specific practical patient management question not answered adequately to date by any combination of these factors for a carefully defined group of patients with node-negative, ER+/HER2- breast cancer (2). The recently published comparative study in the OPTIMA trial addressed the agreement between risk classification based on multigene tests and immunohistochemistry, showing a similar discordance trend between these assays as in our study (1,4).

Retrospective clinical trials/studies correlating gene expression profiling and biomarker profiles with patient survival are excellent tools to prove prognostic value not only for multigene tests but also for commonly used diagnostic assays as IHC. Dr. Suthers correctly cites data from the retrospective TransATAC study providing heterogeneous prognostic information on six measurements including multigene tests on the same tumor tissue such as RS, EPClin (Endopredict), ROR (Prosigna), BCI (Breast Cancer Index) and also IHC and CTS (Clinical Treatment Score) against observed recurrence risk (6). As previously noted in the OPTIMA trial and observed in our study, all these assays had been constructed and validated on different patient cohorts including heterogeneous clinical, nodal and demographic status resulting in different classification power of the individual assays even though the test is carried on the same tumor sample (1,4).

With respect to Dr. Suthers' reference to the Danish Breast Cancer Group 77B study (7), we point out that this level 2 evidence reporting lack of benefit for adjuvant cyclophosphamide monotherapy or CMF is based on 134 patients who received chemotherapy, and 31 who did not. The study, conducted in 1979, was agnostic to any receptor status, and premenopausal women received no adjuvant endocrine therapy. The Luminal A definition applied (ER and or PR >1%/HER2-negative with PR>20% and Ki67 <14% was very sensitive to the PR cut-point chosen. The authors themselves, in their extensive summary of limitations and caveats, cite that "compared to genomics-based nucleic acid tests, immunohistochemical surrogate

panels do not provide as much prognostic information", and "do not have the same level of analytical reproducibility".

We feel that currently available multigene tests should not be used interchangeably nor applied in parallel on the same patient's tissue and that incorporation of risk score classification in treatment decision should be done in the context of what the parent prospective randomized clinical or retrospective comparative trials can responsibly inform the user about (i.e. prognosis versus prediction in a clearly defined population with a relevant, contemporary treatment regimen). Retrospective comparison of multigene tests on the same tissue sample can be easily misinterpreted if the risk score interpretation is taken out of the context from how the assay was constructed and validated.

References:

1) Varga Z, Sinn P, Seidman AD: Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer.
Int J Cancer. 2019 Jan 17. doi: 10.1002/ijc.32139.

2) Sparano JA, Gray RJ, Makower DF et al: Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer.
N Engl J Med. 2018 Jul 12;379(2):111-121. doi: 10.1056/NEJMoa1804710.

3) Cardoso F, van't Veer LJ, Bogaerts et al.: 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer.
N Engl J Med. 2016 Aug 25;375(8):717-29. doi: 10.1056/NEJMoa1602253.

4) Bartlett JM, Bayani J, Marshall A et al: Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others.
J Natl Cancer Inst. 2016 Apr 29;108(9). pii: djw050. doi: 10.1093/jnci/djw050

5) Sestak J, Buus R, Cuczik J et al.: Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial.
JAMA Oncol. 2018 Apr 1;4(4):545-553. doi: 10.1001/jamaoncol.2017.5524.

6) Krop I, Ismaila N, Andre F et al : Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer : American Society of Clinical Oncology Clinical Practice Guideline Focused Update.
J Clin Oncol. 2017 Aug 20;35(24):2838-2847. doi: 10.1200/JCO.2017.74.0472. Epub 2017 Jul 10

7) Nielsen TO, Jensen MJ, Burugu S et al: High-risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant cyclophoshamide-based chemotherapy: results from the DBCG77B clinical trial.
Clin Cancer Res 23(4):946-53, 2017.